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(54) Treatment of migraine

(57) A pharmaceutical composition for the treatment of migraine comprises an effective amount of a local anesthetic and a 5-HT1D agonist. The local anesthetic is preferably benzocaine, mepivacaine, bupivacaine, cocaine, lidocaine or prilidocaine whilst the agonist may be rizatriptan, sumitriptan, naratriptan or zolmitriptan. The composition is advantageously in a form for intranasal administration.

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TITLE

PHARMACEUTICAL PREPARATION

BACKGROUND OF THE INVENTION

The present invention relates to the co-administration, either simultaneously, separately or sequentially of a 5-HT1D agonist and a local anesthetic for use in treating and terminating migraine in a patient in need thereof. This invention also relates to a pharmaceutical formulation which comprises a 5-HT1D agonist and a local anesthetic along with a pharmaceutically acceptable carrier.

Migraine is a recurrent, often familial symptom complex of periodic attacks of vascular headache, which is often associated with nausea and vomiting. Attacks are preceded by constriction of the cranial arteries and commence with vasodilatation. (Dorland's Illustrated Medical Dictionary) 27th 3d, W. B. Saunders Co., 1988). Migraine affects approximately 17% of adult women and 6% of adult men. Stewart W.F., Shechter A, Rasmussen, B.K. "Migraine prevalence: a review of population-based studies", Neurology, 1994, 44(suppl. 4) S17-S23.

Treatment regiments include the use of OTC analgesics, prescription analgesics, ergotamine and derivatives, combination drugs, administration of parenterally, orally and intranasally active 5-HT1D compounds and intranasal administration of lidocaine.

5-HT1D agonists are believed to have three modes of action in the treatment of migraine. First, 5-HT1D agonists constrict dilated intracranial extracerebral arteries and mechanically reduce the pressure of the vessel, thus decreasing the stimulating signals to the sensory nerves around the vessels. Second, 5-HT1D agonists decrease the release of vasoactive peptides, which are the messengers in vasodilatation and sterile inflammation. These two processes are found to play a major role in the pathogenesis of migraine. Third, 5-HT1D agonists lessen the central nociceptive neurtransmission in the trigeminal sensory pathways thus reducing the impulses sent to ganglions. This is apparently effective since the changes in cerebral blood flow induced by

trigeminal stimulation are believed to be mediated by the sphenopalatine ganglion (SPG).

Local anesthetics recently have been studied in clinical trials for use in the treatment of migraine. This treatment is apparently based on the ability to block the conduction of pain impulses. By "numbing" the SPG, lidocaine is believed to interrupt the painful impulses coming from the sensory nerves. The use of lidocaine in the temporary treatment of migraine has been reported by Kudrow et al. (Kudrow, L., Kudrow, D., Sandweiss, J. H. "Rapid and sustained relief of migraine attacks with intra-nasal lidocaine", Headache, 1995; 35, 79-82.) and its effects have again been reported in a randomized, double-blind controlled trial by Maizels, et al. (Maizels, m., Scott, B., Cohen, W., Chen, W., "Intranasal Lidocaine for Treatment of Migraine", JAMA, July 24/31, 1996, Vol 276, No. 4, 319-321.

The time to onset of action of an intranasal local anesthetic such as lidocaine, ranges from about 5 minutes to about 15 minutes. However, the lidocaine has, at best, a moderate duration of action and its effect usually terminates within one hour after administration. As a result, when lidocaine was studies in patients with migraine, 42% reported recurrence of the migraine headache within one hour. The onset of action time for oral and intranasal 5-HT1D agonists ranges from about 30 minutes to about 2 hours. Recurrence of migraine, while reported by about 40% of those studied, was observed within 24 hours after administration of drug.

What is needed is a formulation and method of treatment that provides for rapid onset of action to combat migraine when it is first realized, as well as a method of treatment and formulation which provides for sustained action that prevents reccurrence.

SUMMARY OF THE INVENTION

A method is presented for use in treating and terminating migraine in a patient in need thereof, which comprises the co-administration, either simultaneously, separately or sequentially of a 5-HT1D agonist and a local anesthetic. This invention also relates to a

pharmaceutical formulation which comprises a 5-HT1D agonist and a local anesthetic along with a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

A method is presented for use in treating and terminating migraine in a patient in need thereof, which comprises the co-administration, either simultaneously, separately or sequentially of a 5-HT1D agonist and a local anesthetic. This invention also relates to a pharmaceutical formulation which comprises a 5-HT1D agonist and a local anesthetic along with a pharmaceutically acceptable carrier.

By "migraine" is meant symptom complex occurring periodically and characterized by pain in the head (usually unilateral), vertigo, nausea and vomiting, photophobia, and scintillating appearances of light (Steadman's medical dictionary, 25th edition).

By "co-administration" is meant that both a 5-HT1D agonist and a local anesthetic will be administered to a patient, within a reasonable period of time. The compounds may be in the same pharmaceutically acceptable carrier and therefore administered simultaneously. They may be in separate pharmaceutical carriers such as intranasal sprays or drops and administered either simultaneously, by mixing the materials just prior to administration or in different dosage forms such as a spray and a tablet which are taken simultaneously. The term "co-administration" also refers to the case where the compounds are provided in separate dosage forms and are administered sequentially. Therefore, by way of example, the local anesthetic may be administered as an intranasal drop or spray and then within a reasonable period of time, the 5-HT1D agonist may be administered either as a intranasal spray, intranasal drop or via an oral dosage form.

By "reasonable period of time" is meant a time period that is not in excess of about 1 hour. That is, for example, if the local anesthetic is provided as intranasal drops, then within one hour, the 5-HT1D agonist should be administered, either in the same type of dosage form, or another dosage form which provides effective delivery of the medicament.

By "local anesthetic" is meant a compound that provides anesthesia on any accessible tissue or nerve with which it comes in direct contact. Non-limiting examples of "local anesthetics" which are within the scope of this invention include, but are not limited to, benzocaine, mepivacaine, bupivacaine, cocaine, lidocaine, prilidocaine and the pharmaceutically active salts, acids and bases of these compounds. An example of an acid form of a local anesthetic is lidocaine hydrochloride. Lidocaine hydrochloride may be substituted throughout when the compound lidocaine is encountered.

Certain of the 5-HT1D compounds which are within the scope of this invention may be prepared by processes which are disclosed in United States Patent No. 5,290,520; European Patent Application No. 0,313,397; 0,573,221; United Kingdom Patents Nos. 2,124,210; 2,162,522; and PCT Application No. WO 91/18897; all of which are hereby incorporated by reference. Certain of these synthesis are provided in the Example section for ease of reference. Examples of the 5-HT1D compounds useful in this method of treatment and this formulation are rizatriptan; sumitriptan, naratriptan and zolmitriptan.

In one embodiment of this invention, the local anesthetic is lidocaine and the 5-HT1D agonist is rizatriptan which are provided in separate intranasal formulations containing from about 1% to about 6% lidocaine and from about 2% to about 15% of rizatriptan. The preferred regiment requires the delivery of from about 0.1 to about 1.0 mL of each formulation to be delivered to the inside of one nostril, where the local anesthetic is delivered first and then the 5-HT1D agonist is dispensed.

In an other preferred embodiment of this invention, lidocaine is delivered from an intranasal formulation while rizatriptan is delivered using a fast dissolving oral formulation. By a "fast dissolving oral formulation" is meant, an oral delivery form which when placed on the tong of a patient, dissolves within 10 seconds.

Other preferred embodiments include the delivery of

the topical anesthetic using an intranasal formulation and the delivery of the 5-HT1D agonist as a conventional tablet, liquid, elixer or suspension. For example, lidocaine may be delivered through an intranasal formulation while sumatriptan, naratriptan or zolmitriptan may be delivered as tablets, oral suspensions or other dosage forms.

In the most preferred embodiment of this invention, the local anesthetic, such as lidocaine, and the 5-HT1D agonist, such as rizatriptan, are present in the same intranasal formulation. This formulation is dispensed into one nostril in a volume of from about 0.1 mL to about 1.0 mL. The formulation may consist of either one pharmaceutically suitable carrier solution which contains both the local anesthetic and the 5-HT1D agonist, or in the alternative, two separate pharmaceutically suitable carrier solutions may be provided in a device which provides for simultaneous delivery of each intranasally, from separately stored preparations. In this manner, different volumes of each solution may be sprayed or added drop-wise into the nostril simultaneously.

When the sulfate salt of rizatriptan, which is N,N-dimethyl-2-[5-(1,2,4-triazol-1-yl-methyl)-1H-indol-3-yl]ethylamine is used as the 5-HT1D agonist, the preferred dosage is from about 0.1 mg to about 100 mg, or more preferably from about 1 to about 60 mg and most preferably from about 1 to about 35 mg of rizatriptan sulfate administered in a single dose to one nostril. When lidocaine is used as the local anesthetic, from about 0.5 to about 5 mg or most preferably from about 1 mg to about 3 mg of lidocaine is administered in a single dose to one nostril. This dosage is most preferably delivered using a pharmaceutically acceptable intranasal carrier which ranges in volume from about 0.1 mL to about 1.0 mL.

As can easily be seen from the description of the preferred embodiments of this invention, any of the above mentioned compounds in the combinations described are considered within the scope of this invention.

As previously stated, the time of onset of action of most local anesthetics ranges from about 5 to about 15 minutes and the

average onset of action of most oral and intranasal 5-HT1D agonists ranges from about 30 minutes to about 2 hours. Locally compounds such as lidocaine have a vasodilatative effect. This means that the absorption of the 5-HT1D agonist will be enhanced by the dilated blood vessels when the two compounds are given together. The increased absorption leads to faster distribution and onset of action of the 5-HT1D agonist. which has a systemic mechanism of action.

Lidocaine has a moderate duration of action. Usually the duration of action ends within one hour. This explains the recurrence of migraine headache in 42% of the patients tested, who complained that their migraine reoccurred within the first hour following treatment with lidocaine.

5-HT1D agonists have a systemic mechanism of action. While the rate of headache recurrence with 5-HT1D agonists is approximately 40% within a 24 hour period, the overall recurrence rate will decrease when both compounds are administered together in the treatment of migraine, since the combination will effect the migraine in two different ways. First, the 5-HT1D agonists lessen the signals to the sensory nerves. Second, simultaneously, the local anesthetic blocks sensory nerve conduction. Since the pathogenic circle in migraine is influenced by these two major mechanisms, the chances for headache relapse decrease. Separately, patients taking either compound experience recurrence, which probably means the mechanism that is not suppressed allows for return of the headache. When a local anesthetic and a 5-HT1D agonist are both used in the treatment of migraine, both mechanisms will be suppressed and the duration of action in the treatment of migraine will therefore be increased.

As noted previously, this invention also provides pharmaceutical compositions comprising one or more of the 5-HT1D agonist compounds of this invention and one or more of the local anesthetics of this invention in association with a pharmaceutically acceptable carrier. These compounds may be combined in the same dosage form or may be delivered in separate dosage forms. Preferably these compositions are formulated together in a liquid pharmaceutical

carrier which is designed for intranasal administration. The intranasal formulation is administered as either a drop or spray such that the local anesthetic makes contact with and anesthetizes the sphenopalatine ganglion (SPG) which resides just posterior to and immediately above the posterior tip of the middle turbinate, beneath the nasal mucosa. In a manner similar to the study of Maizels et al., the optimum effect will be observed when the lidocaine and 5-HT1D intranasal formulation is administered with the patient in a supine position with the head hyperextended 45° and rotated 30° to the side of the headache. Co-administration of the local anesthetic and the 5-HT1D agonist in this manner assures enhancement of absorption of the 5-HT1D agonist and reduces the onset of action time of the 5-HT1D agonists.

Alternatively, separate intranasal formulations of both the 5-HT1D agonist and the local anesthetic may be desired. Here, the most preferred formulation relies on the delivery of these compounds as intranasal drops or spray which are able to reach the area of the SPG. The local anesthetic is delivered first followed, within a reasonable period of time by the 5-HT1D agonist.

In a less preferred formulation, the local anesthetic, such as lidocaine, may be delivered using an intranasal formulation as above and the 5-HT1D agonist may be dispensed using any of tablets, pills, capsules, powders, granules, sterile parenteral solutions, fast dissolving oral dosage forms or suspensions, for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the 5-HT1D agonist is

dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the 5-HT1D agonist and from about 0.01 to about 1 mg of local anesthetic. The tablets of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The oral liquid forms in which the 5-HT1D agonists may be incorporated include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of migraine, a suitable oral dosage level for the 5-HT1D agonist is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. A suitable dosage level for the local anesthetic is about 0.01 to 1000 µg/kg per day, and especially about 0.2 to about 500 µg/kg per day and especially about 0.4 to about 250 µg/kg/day. The compounds may be administered on a regimen of 1 to 4 times per day.

EXAMPLES

EXAMPLE 1

2-[5-(2-Benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

1. 4-Hydrazinobenzylcyanide. Hydrochloride

A solution of $NaNO_2$ (80 g, 1.16 mol) was added dropwise to a cooled (-10°C), stirred, suspension of 4-aminobenzyl cyanide (153.5g, 1.16mol) in concentrated HCl (1500ml), at such a rate that the temperature did not rise above -10°C. The mixture was stirred at -10°C for 0.25h before being filtered rapidly under vacuum into an addition funnel. The solution was added portionwise over a 0.25h period to a rapidly stirred mixture of $SnCl_2.2H_2O$ (1.05kg, 4.64mol) in concentrated HCl (800 ml) keeping the temperature below -5°C. The mixture was allowed to warm to room temperature and stir for 0.25h before filtering the sandy colored precipitate under vacuum and washing with ether (5 x 500 ml). The resultant solid was dried over P_2O_5 in a vacuum oven (80°C) for 16h to give the title compound (213g, 100%), m.p. 181-183°C; ^1H NMR (360MHz, D_2O) δ 3.90 (2H, s, CH_2); 7.06 (2H, d, J = 8.7Hz, Ar-H); 7.40 (2H, d, J = 8.7Hz, Ar-H).

2. 2-(5-Cyanomethyl-1H-indol-3-yl)ethylamine. Hydrochloride

4-Chlorobutanal dimethylacetal (37.07g, 0.24 mol) was added to a stirred solution of 4-hydrazinobenzyl cyanide hydrochloride (47.0g, 0.26 mol) in EtOH/H_2O (5:1; 21) and refluxed for 4.5h. The reaction mixture was evaporated to dryness under vacuum, MeOH (150 ml) added, and the mixture left at 0°C for 10h. The resultant pale yellow precipitate was filtered under vacuum, washed with Et_2O/MeOH (5:1; 2 x 100 ml) and dried. The product was used without further purification (24.1g, 40%), m.p. 239-241°C; R_f 0.4 in CH_2Cl_2/EtOH/NH_3 (40:8:1); ^1H NMR (360MHz, D_2O) 3.18 (2H, t, J = 7.1Hz, CH_2); 3.36 (2H, t, J = 7.1Hz, CH_2); 4.02 (2H, s, CH_2); 7.22 (1H,

dd, J = 1.5 and 8.4Hz, Ar-H); 7.36 (1H, s, Ar-H); 7.56 (1H, d, J = 8.4Hz, Ar-H); 7.66 (1H, s, Ar-H).

3. 2-(5-Tetrazol-5-ylmethyl-1H-indol-3-yl) ethylamine

A solution of 2-(5-cyanomethyl-1H-indol-3-yl) ethylamine hydrochloride (2.5g, 10.6 mmol), triethylamine hydrochloride (2.2g, 16.0 mmol) and sodium azide (2.1g, 32.3 mmol), in 1-methylpyrrolidin-2-one (30 ml) was heated at 140°C for 8h. 5N hydrochloric acid (3 ml) was added and the solvents removed by distillation under vacuum. The residue was chromatographed on silica-gel eluting with $EtOH/Et_2O/H_2O/NH_3$ (20:30:8:1) to give the title-tetrazole (1.76g, 69%); δ (360MHz, CD_3OD) 3.06 (2H, t, J = 7.2Hz, CH_2); 3.19 (2H, t, J = 7.2Hz, CH_2); 4.29 (2H, s, CH_2); 7.07 (1H, d, J = 8.4Hz, Ar-H); 7.13 (1H, s, Ar-H); 7.29 (1H, d, J = 8.4Hz, Ar-H); 7.44 (1H, s, Ar-H).

4. N-tert-Butyloxycarbonyl-2-(5-tetrazol-5-ylmethyl-1H-indol-3-yl)ethylamine

To a stirred suspension of 2-(5-tetrazol-5-ylmethyl-1H-indol- 3-yl)ethylamine (1.76g, 7.27 mmol) in dry CH_2Cl_2 (40 ml) was added triethylamine (1.5g, 14.9 mmol) and $(BOC)_2O$ (1.9g, 7.3 mmol) and the mixture stirred for 16 h. The solvent was removed under vacuum and the residue chromatographed on silica-gel eluting with $EtOH/Et_2O/H_2O/NH_3$ (20:60:8:1) to give the title product (1.6g, 64%); δ (360MHz, CD_3OD) 1.41 (9H, s, 3 of CH_3); 2.87 (2H, t, J = 7.4 Hz, CH_2); 3.30 (2H, t, J = 7.4 Hz, CH_2); 4.32 (2H, s, CH_2); 6.99 (1H, d, J = 8.3 Hz, Ar-H); 7.04 (1H, s, Ar-H); 7.26 (1H, d, J = 8.3 Hz, Ar-H); 7.49 (1H, s, Ar-H).

5. N-tert-Butyloxycarbonyl-2-[5-(2-benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine and N-tert-butyloxycarbonyl-2-[5-(1-benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine

Benzyl bromide (0.31 g, 1.8 mmol) was added to a solution of the tetrazole from step 4 (0.62g, 1.8 mmol), and triethylamine (0.37g, 3.6 mmol) in dry acetonitrile (20 ml). The mixture was stirred at R.T. for 2h, heated at 70°C for 1h and then stirred at R.T. for 16 h. The solvent was removed under vacuum and the residue chromatographed through silica-gel eluting with CH_2Cl_2/MeOH (97:3) to give 2-separated benzyl tetrazoles. The less polar isomer was identified as the 2-benzyl tetrazole (0.17g, 22.4%); δ (360MHz, $CDCl_3$) 1.43 (9H, s, 3 of CH_3); 2.90 (2H, t, J = 6.8Hz, CH_2); 3.41 (2H, br t, CH_2); 4.32 (2H, s, CH_2); 5.70 (2H, s, CH_2Ph); 7.00 (1H, s, Ar-H); 7.15 (1H, d, J = 8.4Hz, Ar-H); 7.28 (1H, d, J = 8.4Hz, Ar-H); 7.34 (5H, s, Ar-H); 7.50 (1H, s, Ar-H); 7.96 (1H, br s, NH).

The more polar component was identified as the 1-benzyltetrazole (0.2g, 26.4%) δ (360MHz, $CDCl_3$) 1.43 (9H, s, 3 of CH_3); 2.88 (2H, t, J = 7.0Hz, CH_2); 3.40 (1H, br t, CH_2); 4.26 (2H, s, CH_2); 5.29 (2H, s, CH_2-Ph); 6.92 (1H, d, J = 8.4Hz, Ar-H); 7.01-7.05 (3H, m, Ar-H); 7.27-7.30 (5H, m, Ar-H); 8.08 (1H, br s, NH).

6. 2-[5-(2-Benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

Trifluoroacetic acid (1.5 ml) was added to a solution of the less polar component isolated from step 5 (0.17g, 0.4 mmol) in CH_2Cl_2 (5 ml) and stirred at R.T. for 1h. The solvents were removed under vacuum and the residue chromatographed through silica-gel eluting with CH_2Cl_2/EtOH/NH_3 (40:8:1) to give the title-tetrazole. The oxalate salt was prepared (65 mg); mp 169-171°C; (Found: C, 59.23; H, 5.07; N, 19.60. $C_{19}H_{20}N_6$.1.05 ($C_2H_2O_4$) requires C, 59.36; H, 5.22; N, 19.68%); δ (360MHz, D_2O) 3.09 (2H, t, J = 6.9 Hz, CH_2); 3.29 (2H, t, J = 6.9 Hz, CH_2); 4.30 (2H, s, CH_2); 5.77 (2H, s, CH_2); 7.11 (1H, dd, J = 1.6 and 8.4Hz, Ar-H); 7.28 (1H, s, Ar-H); 7.32-7.34 and 7.39-7.41 (5H, m, Ar-H); 7.43 (1H, d, J = 8.4Hz, Ar-H); 7.51 (1H, s, Ar-H).

EXAMPLE 2

2-[5-(1-Benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Hydrochloride. Hemihydrate

Prepared from the more polar component isolated from step 5, Example 1, using the procedure described for step 6, Example 1. The hydrochloride hemihydrate salt was prepared; mp 210-213°C; (Found: C, 60.39; H, 5.88; N, 22.14. $C_{19}H_{20}N_6.HCl.0.5H_2O$ requires C, 60.39; H, 5.87; N, 22.24%); δ (250 MHz, D_2O) 3.02 (2H, t, J = 6.8Hz, CH_2); 3.19 (2H, t, J = 6.8Hz, CH_2); 4.44 (2H, s, CH_2); 5.60 (2H, s, CH_2); 6.95-7.02 (3H, m, Ar-H); 7.16-7.25 (4H, m, Ar-H); 7.28 (1H, s, Ar-H); 7.40 (1H, d, J = 8.4Hz, Ar-H).

EXAMPLE 3

N,N-Dimethyl-2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

1. N-tert-Butyloxycarbonyl-2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine and N-tert-butyloxycarbonyl-2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine

Methyl iodide (0.44g, 3.1 mmol) was added to a stirred solution of the tetrazole from step 4, Example 1 (0.95g, 2.78 mmol) and triethylamine (0.56g, 5.5 mmol) in dry acetonitrile (15 ml). After 10 h a further equivalent of methyl iodide was added and stirred for 16h. The solvent was removed under vacuum and the residue chromatographed on silica-gel eluting with CH_2Cl_2/MeOH (97:3) to give the title mixture of 1- and 2-methyltetrazoles (0.6g, 61%); δ (360MHz, $CDCl_3$) 1.43 (9H, m, 3 of CH_3); 2.89-2.92 (2H, m, CH_2); 3.38-3.48 (2H, m, CH_2); 3.83 (2H, s, CH_2); 4.28 and 4.40 (total 3H, s, CH_3); 6.98 and 7.17 (total 1H, d, J = 8.4Hz, Ar-H); 7.02 and 7.06 (total 1H, s, Ar-H); 7.30 and 7.31 (total 1H, d, J = 8.4Hz, Ar-H); 7.43 and 7.54 (total 1H, s, Ar-H); 8.00 and 8.10 (total 1H, br s, NH).

2. 2-[5-(2-Methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine and 2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine

Prepared from the preceding methyltetrazoles using the procedure described in step 6, Example 1. The crude product was chromatographed on silica-gel eluting with CH_2Cl_2/EtOH/NH_3 (40:8:1) to give 2 separated components. The less polar product (0.1g, 24%) was identified as the 2-methyltetrazole; δ (360MHz, $CDCl_3$) 1.38 (9H, s, 3 of CH_3); 2.88 (2H, t, J = 6.6 Hz, CH_2); 3.00 (2H, t, J = 6.6 Hz, CH_2); 4.28 (3H, s, CH_3); 4.33 (2H, s, CH_2); 7.00 (1H, d, J = 8.4Hz, Ar-H); 7.06 (1H, d, J = 2.1 Hz, Ar-H); 7.17 (1H, d, J = 8.4Hz, Ar-H); 7.56 (1H, s, Ar-H); 8.04 (1H, br s, NH).

The more polar product (0.13g, 31%) was identified as the 1-methyltetrazole; δ (360MHz, $CDCl_3$) 1.38 (9H, s, 3 of CH_3); 2.86 (2H, t, J = 6.6 Hz, CH_2); 3.00 (2H, t, J = 6.6 Hz, CH_2); 3.82 (3H, s, CH_3); 4.40 (2H, s, CH_2); 6.98 (1H, dd, J = 1.6 and 8.3 Hz, Ar-H); 7.06 (1H, d, J = 1.6 Hz, Ar-H); 7.31 (1H, d, J = 8.3 Hz, Ar-H); 7.41 (1H, s, Ar-H); 8.18 (1H, br s, NH).

3. N,N-Dimethyl-2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

A solution of formaldehyde (80 mg of a 30% solution) in methanol (15 ml) was added to a stirred solution of 2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine (0.1g, 0.4mmol), $NaCNBH_3$ (60 mg) and glacial acetic acid (0.12g) in methanol (15 ml). The solution was stirred for 2h, basified with K_2CO_3 solution and the MeOH removed under vacuum. The crude product obtained after extraction into ethylacetate and removal of solvent was chromatographed through silica-gel eluting with CH_2Cl_2/EtOH/NH_3 (40:8:1) to give the desired N,N-dimethyl-tryptamine (96 mg, 87%). The oxalate salt was prepared: mp 185-187°C (MeOH/Et_2O); (Found: C, 54.42; H, 5.74; N, 22.53.

$C_{15}H_{20}N_6.C_2H_2O_4$ requires C, 54.54; H, 5.92; N, 22.45%); δ (360MHz, D_2O) 2.91 (6H, s, 2 of CH_3); 3.21 (2H, t, J = 7.4 Hz, CH_2); 3.47 (2H, t, J = 7.4 Hz, CH_2); 4.30 (3H, s, CH_3); 4.34 (2H, s, CH_2); 7.17 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.33 (1H, s, Ar-H); 7.48 (1H, d, J = 8.4Hz, Ar-H); 7.59 (1H, s, Ar-H).

EXAMPLE 4

N,N-Dimethyl-2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

Prepared from 2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine (0.125g, 0.49 mmol) using the procedure described in step 3, Example 3. The free base (0.11g, 80%) obtained was converted to the oxalate salt and recrystallized from MeOH/Et_2O; mp 176-177°C; (Found: C, 54.21; H, 5.84; N, 22.36. $C_{15}H_{20}N_6.C_2H_2O_4$ requires C, 54.54; H, 5.92; N, 22.45%); δ (360MHz, D_2O); 2.91 (6H, s, 2 of CH_3); 3.21 (2H, t, J = 7.4 Hz, CH_2); 3.40 (2H, t, J = 7.4 Hz, CH_2); 4.00 (3H, s, CH_3); 4.43 (2H, s, CH_2); 7.13 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.35 (1H, s, Ar-H); 7.50 (1H, d, J = 8.4Hz, Ar-H); 7.54 (1H, s, Ar-H).

EXAMPLE 5

N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine Oxalate Hemihydrate

1. 1-(4-Nitrophenyl)methyl-1,2,4-triazole

4-Nitrobenzylbromide (21.6g, 0.1 mol) was added to a rapidly stirred suspension of 1,2,4-triazole sodium salt (9.1g, 0.1 mol) in anhydrous DMF (100 ml) and the mixture stirred at room temperature for 16h. Ethyl acetate (400 ml) was added followed by water (250 ml) and the layers separated. The organic phase was washed with water (3 x 250 ml), dried ($MgSO_4$) and evaporated. The residue was

chromatographed on silica gel eluting with ethyl acetate to give the title-product (10.6 g, 52%); m.p. 98-100°C. δ (360MHz, $CDCl_3$) 5.47 (2H, s, CH_2) 7.40 (2H, d, J = 9 Hz, Ar-H), 8.02 (1H, s, Ar-H), 8.18 (1H, s, Ar-H), 8.23 (2H, d, J = 9 Hz, Ar-H).

2. 1-(4-Aminophenyl)methyl-1,2,4-triazole. Hydrochloride

A solution of 1-(4-nitrophenyl)methyl-1,2,4-triazole (10.0g, 49 mmol) in ethanol (50 ml), ethyl acetate (50 ml), 5N HCl (10 ml) and water (10 ml) was hydrogenated over 10% Pd/C (1.0g) at 40 p.s.i., in a Parr apparatus, until an uptake of 188 p.s.i., had been observed (approximately 10 mins). The catalyst was removed by filtration through hyflo and the solvent removed under vacuum. The residue was azeotroped with ethanol (x2) to give the title-amine hydrochloride (10.6g, 100%). δ (360MHz, D_2O) 5.53 (2H, s, CH_2), 7.37-7.48 (4H, m, Ar-H), 8.12 (1H, s, Ar-H), 8.66 (1H, s, Ar-H).

3. 1-(4-Hydrazinophenyl)methyl-1,2,4-triazole

A solution of sodium nitrite (3.28g, 48 mmol) in water (20 ml) was added to a solution of the preceding amine hydrochloride (10.0g, 48 mmol), in concentrated HCl (40 ml), at such a rate that the temperature did not exceed -10°C. After addition was complete the solution was stirred at 0°C for 0.25h and then added portionwise to a rapidly stirred solution of $SnCl_2.2H_2O$ (40g) in concentrated HCl (40 ml). The solution was warmed to room temperature and basified with 20% aqueous NaOH solution. The solution was extracted with ethyl acetate (3 x 250 ml) and the combined extracts dried ($MgSO_4$) and filtered through hyflo. The solution was evaporated to dryness to give the desired hydrazine (5.0g, 56%) m.p. 109-112°C. δ (360MHz, D_6-DMSO) 3.93 (2H, br s, NH_2), 5.20 (2H, s, CH_2), 6.73 (2H, d, J = 8Hz, Ar-H), 7.08 (2H, d, J = 8Hz, Ar-H), 7.92 (1H, s, Ar-H), 8.57 (1H, s, Ar-H).

4. 2-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl] ethylamine.

4-Chlorobutanal dimethylacetal (3.22 g, 21.1 mmol) was added to a stirred solution of the preceding hydrazine (5.0 g, 26.4 mmol) in ethanol/water (5:1, 180 ml) and 5N HCl (4.5 ml) and the solution refluxed for 4 h. The solvents were removed under vacuum and the residue chromatographed on silica gel, eluting with CH_2Cl_2/EtOH/NH_3 (30:8:1) to give the desired tryptamine (2.4g, 38%). δ(360MHz, $CDCl_3$) 2.90 (2H, t, J = 7Hz, CH_2), 2.99 (2H, t, J = 7Hz, CH_2), 5.43 (2H, s, CH_2), 7.10 (1H, s, Ar-H), 7.11 (1H, d, J = 8Hz, Ar-H), 7.39 (1H, d, J = 8Hz, Ar-H), 7.57 (1H, s, Ar-H), 7.94 (1H, s, Ar-H), 8.08 (1H, s, Ar-H).

5. N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine Oxalate Hemihydrate

A solution of formaldehyde (37% w/w solution, 0.19 g), in methanol (10 ml), was added to a mixture of the preceding tryptamine (0.36 g, 1.5 mmol), $NaCNBH_3$ (0.225 g, 3.6 mmol) and glacial acetic acid (0.45 g), in methanol (10 ml). The mixture was stirred at room temperature for 2h before adding saturated K_2CO_3 (50 ml) and evaporating the methanol. The residue was extracted with ethyl acetate (3 x 100 ml) and the combined extracts washed with brine (100 ml), dried (K_2CO_3), and evaporated. The crude product was chromatographed on silica gel eluting with CH_2Cl_2/EtOH/NH_3 (20:8:1) to give the free base of the title compound (0.21 g, 52%). The oxalate hemihydrate salt was prepared, m.p. 165-167°C (MeOH/Et_2O); (Found: C, 55.53; H, 6.04; N, 18.59. $C_{15}H_{19}N_5.C_2H_2O_4$. 0.55 H_2O requires C, 55.29; H, 6.03; N, 18.96%); m/e 269 (M^+); δ (360MHz, D_2O) 2.91 (6H, s, NMe_2), 3.22 (2H, t, J = 7Hz, CH_2), 3.47 (2H, t, J = 7Hz, CH_2), 5.52 (2H, s, CH_2), 7.21 (1H, dd, J = 1.6 and 8.4Hz, Ar-H), 7.36 (1H, s, Ar-H), 7.52 (1H, d, J = 8.4Hz, Ar-H), 7.65 (1H, s, Ar-H), 8.06 (1H, s, Ar-H), 8.56 (1H, s, Ar-H).

EXAMPLE 6

N,N-Dimethyl-2-[5-(1,2,4-triazol-1ylmethyl)-1H-indol-3-yl]ethylamine. Succinate. Procedure B

A solution of 1-(4-hydraziinophenyl)methyl-1,2,4-triazole dihydrochloride (2 g, 7.6 mmol, Example 5 step 3) and 4-N,N-dimethylaminobutanal dimethylacetal (1.8 g, 11.2 mmol) in 4% aqueous sulphuric acid (70 ml) was heated at reflux for 2h. After the reaction mixture was cooled to room temperature, ethyl acetate (200 ml) was added and the aqueous basified with K_2CO_3. The aqueous was separated and extracted further with ethyl acetate (2 x 150 ml). The combined organics were dried (Na_2SO_4) and evaporated, and the residue chromatographed on silica gel eluting with CH_2Cl_2/EtOH/NH_3 (30:8:1) to give the title-triazole (610 mg, 30%). The succinate salt was prepared by addition of a solution of succinic acid (0.27g, 2.3 mmol) in methanol (3 ml) to a solution of the triazole (0.61g, 2.3 mmol) in methanol (5 ml). The solvent was removed under vacuum and the resultant product recrystallised from isopropylalcohol, mp 118-120°C;

(Found: C, 58.76; H, 6.27; N, 17.79. $C_{15}H_{19}N_3.C_4H_6O_4$ requires C, 58.90; H, 6.50; N, 18.08%).

EXAMPLE 7

N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine Benzoate

The benzoate salt of N,N-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)- 1H-indol-3-yl]ethylamine was prepared by addition of a solution of benzoic acid in diethyl ether to a solution of the free base in ethanol/diethyl ether (1:4). The precipitated salt was recrystallised from ethanol, mp 178-180°C;

(Found: C, 67.28; H, 6.55; N, 17.66. $C_{15}H_{19}N_3.C_6H_5CO_2H$ requires C, 67.50; H, 6.44; N, 17.89%); ^{1}H NMR (360MHz, D_2O) δ 2.92 (6H, s, NMe_2); 3.22 (2H, t, J = 7.3Hz, CH_2); 3.46 (2H, t, J = 7.3Hz, CH_2); 5.52 (2H, s, CH_2); 7.22 (1H, dd, J = 1.6 and 8.4Hz, Ar-H); 7.36 (1H, s, Ar-H); 7.44-7.58 (4H, m, Ar-H); 7.65 (1H, s, Ar-H); 7.87-7.91 (2H, m, Ar-H); 8.06 (1H, s, Ar-H); 8.54 (1H, s, Ar-H).

EXAMPLE 8

Tablet Preparation

Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0 and 100.0 mg, respectively of the following compounds are prepared as illustrated below:

N,N-Dimethyl-2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate.

N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Benzoate.

N,N-Dimethyl-2-[5-(1,2,3,4-tetrazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Succinate.

N-Methyl-4-[5-imidazol-1-yl-1H-indol-3-yl]piperidine. Sesquioxalate.

N-Methyl-3-[5-(1,2,3-triazol-1-yl)-1H-indol-3-yl]pyrrolidine. Oxalate.

TABLE FOR DOSES CONTAINING FROM 1-25 MG OF THE ACTIVE COMPOUND

	Amount-mg		
Active Compound	1.0	2.0	25.0
Microcrystalline cellulose	49.25	48.75	37.25
Modified food corn starch	49.25	48.75	37.25
Magnesium stearate	0.50	0.50	0.50

TABLE FOR DOSES CONTAINING FROM 26-100 MG OF THE ACTIVE COMPOUND

	Amount-mg		
Active Compound	26.0	50.0	100.0
Microcrystalline cellulose	52.0	100.0	200.0
Modified food corn starch	2.21	4.25	8.5
Magnesium stearate	0.39	0.75	1.5

All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0 mg, 2.0 mg, 25.0 mg, 26.0 mg, 50.0 mg and 100 mg of the active ingredient per tablet.

EXAMPLE 9

Intranasal Formulation Containing Lidocaine

An intranasal formulation containing lidocaine is prepared by dissolving 4g of lidocaine hydrochloride in 100 mL of sterile saline, to provide a 4% solution. This formulation is then dispensed in drops

directly into the nostril of the patient. Each drop which occupies a volume of about 0.05 mL contains approximately 2 mg of lidocaine. From about 1 to about 20 drops of this solution is delivered to the nostril of the patient in the manner previously described.

EXAMPLE 10

Synthesis Of Rizatriptan Sulfate (N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. 0.5 sulphate. 0.7 hydrate)

Sulphuric acid (1N, 1.17 ml) was added to a stirred solution of N,N-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine (0.63 g, 2.34 mmole) in water (0.73 ml) and isopropyl alcohol (15.9 ml). The mixture was seeded, then cooled to 0°C. The reaction mixture was filtered and the solid product washed with diethyl ether (100 ml) and then dried at 60°C in vacuo to give the title 0.5 sulphate salt (0.68 g), m.p. 233-234°C.

(Found: C, 54.45; H, 6.35; N, 21.23; S, 4.66%. $C_{15}H_{19}N_5$. 0.5 H_2SO_4. 0.7 H_2O requires C, 54.43; H, 6.52; N, 21.16; S, 4.84%).

EXAMPLES 11 - 14

Intranasal Formulation Containing Lidocaine And Rizatriptan

Sterile Intranasal Formulation

	Example 11	Example 12
Rizatriptan	5 mg	50 mg
Sulphuric Acid (conc.) BP	0.91 mg	9.1 mg
Bulk Water for Injections Ph. Eur.	to 1 ml	to 1 ml
Lidocaine	4 mg	6 mg

	Example 13	Example 14
Rizatriptan	100 mg	160 mg
Sulphuric Acid (conc.) BP	18.2 mg	29.1 mg
Bulk Water for Injections Ph. Eur.	to 1 ml	to 1 ml
Lidocaine	4 mg	6 mg

The rizatriptan is dissolved in the sulphuric acid previously diluted with water. The lidocaine is then dissolved in the resulting solution. The solution is made up to volume.

The formulations are filled into vials in 100 µl aliquots, the vials are sealed and are sterilized by autoclaving to 121°C for not less than 15 minutes. Alternatively, the solutions may be sterilized by filtration and filled aseptically into sterile vials.

The formulations are administered in unit dose volumes of 100 µl to a single nostril of patients suffering from a moderate or severe migraine attack to deliver a dose of 0.5, 5, 10 or 16 mg of the compound of formula (II).

WHAT IS CLAIMED IS:

1. A method of treating migraine which comprises the co-administration to a patient in need of such treatment of an effective amount of a local anesthetic and a 5-HT1D agonist.

2. The method of Claim 1, wherein the local anesthetic is selected from benzocaine, mepivacaine, bupivacaine, cocaine, lidocaine and prilidocaine and the pharmaceutically active salts, acids and bases of these compounds.

3. The method of Claim 2, wherein the local anesthetic is lidocaine hydrochloride.

4. The method of Claim 1, wherein the 5-HT1D agonist is selected from rizatriptan, sumitriptin, naratriptan or zolmitriptan.

5. The method of Claim 1, wherein the 5-HT1D agonist is rizatriptan.

6. An intranasal formulation for the treatment of migraine which comprises a local anesthetic and a 5-HT1D agonist.

7. The formulation of Claim 6 wherein the local anesthetic is selected from benzocaine, mepivacaine, bupivacaine, cocaine, lidocaine and prilidocaine and the pharmaceutically active salts, acids and bases of these compounds.

8. The formulation of Claim 7, wherein the local anesthetic is lidocaine hydrochloride.

9. The formulation of Claim 6, wherein the 5-HT1D agonist is selected from rizatriptan, sumitriptin, naratriptan or zolmitriptan.

10. The formulation of Claim 9, wherein the 5-HT-1D agonist is rizatriptan.

11. The intranasal formulation of Claim 6, which comprises from about 1 to about 35 mg of rizatripan and from about 1 to about 3 mg of lidocaine in a pharmaceutically acceptable intranasal carrier which ranges in volume from about 01 mL to about 1.0 mL.

12. A method of terminating migraine which comprises the co-administration to a patient in need of such treatment of an effective amount of a local anesthetic and a 5-HT1D agonist.

13. The method of Claim 12, wherein the local anesthetic is selected from benzocaine, mepivacaine, bupivacaine, cocaine, lidocaine and prilidocaine and the pharmaceutically active salts, acids and bases of these compounds.

14. The method of Claim 13, wherein the local anesthetic is lidocaine hydrochloride.

15. The method of Claim 12, wherein the 5-HT1D agonist is selected from rizatriptan, sumitriptin naratriptan, or zolmitriptan.

16. The method of Claim 12, wherein the 5-HT1D agonist is rizatriptan.

Patent Office

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Application No:	GB 9715490.0	**Examiner:**	John Jenkins
Claims searched:	1-16	**Date of search:**	17 October 1997

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Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O):

Int Cl (Ed.6):

Other: ONLINE: CAS-ONLINE, WPI, DIALINDEX(MEDICINE)

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
	NONE	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
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